Case Report

Shortness of breath: a common symptom with a rare cause

S Ghosh

Key points

- Acute interstitial pneumonitis is a variant of idiopathic acute respiratory distress syndrome.
- Most common symptoms patient presents with an upper respiratory infection / viral-like prodrome, shortness of breath and a non- productive cough.
- Diffuse alveolar damage can be seen on lung histopathology.
- No specific or proven effective treatments for AIP exist, it is primarily supportive, Multidisciplinary team involvement is best for optional therapy.
- Most deaths (60%) occur within 1-6 months of diagnosis (median survival 1 ½ months).

Case report

A 51-year old Caucasian male was admitted to the hospital with a history of breathlessness of one month duration. Prior to this he had been well. He complained that the shortness of breath had worsened over the previous 10 days and was associated with fatigue and fever. The antibiotics from his GP did not relieve his symptoms. He denied any cough, sputum or haemoptysis.

He had never had any respiratory problems before and was very fit and active. He was an outdoor education instructor by profession, and he climbed high altitudes and enjoyed potholing. His past medical history consisted of a subarachnoid haemorrhage. He was an ex-smoker and had smoked 20 cigarettes a day for approximately 20 years, then intermittently for 10 years and had finally quit 2 years ago. He had no industrial exposure or family history of respiratory disease. He did not have any pets. He had been to France recently.

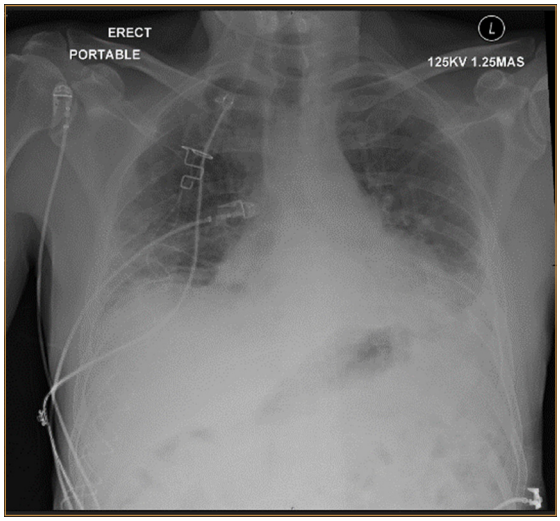

Figure 1. Chest radiograph

On examination, his saturations on air were 90%, his blood pressure was 110/70 mmHg, he was afebrile, had a tachycardia at 100 beats per minute and a respiratory rate of 25 breaths per minute. Clubbing was present. He had bi-basal crepitations through to the mid zones of his lungs more on the right side compared to the left. Heart sounds were normal. Jugular venous pressure was not elevated and there was no calf swelling or oedema. The abdomen was soft, and non-tender, and there was no organomegaly detected.

Investigations

On admission, the blood results were –

Haemoglobin	14.5 g/dl
White blood count	8.1 x 10^9/l
Platelet	564 x 10^9/l
C-reactive protein	163 mg/l
Troponin	0.01 µg/l
Urea and electrolytes	within normal limits
Blood cultures	no growth after 48 hours
Blood gas on 35% oxygen:	pH 7.52, pO2 11.7, pCO2 3.9, HCO3 26.3, BE 1.7, oxygen saturation 98%

Question 1

What are the significant findings on the chest radiograph?

Answer 1

The chest radiograph shows bilateral shadowing, increased lung markings and upper lobe diversion.

The patient was diagnosed with bacterial pneumonia and treatment with antibiotics was started. However despite 6 days of co-amoxiclav

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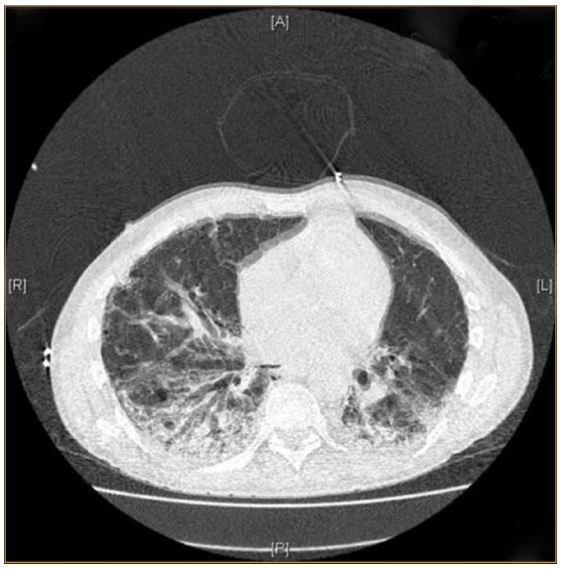

Figure 2.

there was no improvement in his oxygen saturation levels. Macrolide antibiotics were added to cover for atypical pneumonia. Despite escalation of antibiotic to piperacillin-tazobactam (Tazocin) he did not show improvement in his clinical condition. As per microbiology advice, a viral respiratory screen was sent which was negative. He then underwent computerised tomography (CT) to further explore the chest radiograph findings (figure 2).

Question 2

What do you find striking in the CT scan?

Answer 2

The CT scan confirms bi-basal consolidation with air bronchograms. It was felt to be inflammatory rather than infective; there was no evidence of mediastinal lymphadenopathy. The pulmonary artery was of normal dimensions.

An echocardiogram was performed to determine if there was any evidence of cardiac failure. It showed no evidence of pulmonary hypertension – mild left ventricular systolic impairment, normal diastolic function, and a small atrial septal defect. There was no valvulopathy.

Bronchoscopy was carried out in an attempt to isolate a pathogen. During bronchoscopy the patient experienced significant hypoxic episodes requiring nasal high flow oxygen (HFNO), and he was transferred to the High Dependency Unit. Invasive ventilation was considered, but was not indicated as adequate oxygenation was achieved with HFNO. His bronchial washing was negative for cells or organisms. The microbiological results along with the CT scan pointed an inflammatory rather than an infective pathology.

His screen for atypical organisms (Legionella, Q fever, Chlamydia, Mycoplasma), auto-immune screen: Anti-neutrophil cytoplasmic antibody (ANCA); Anti-nuclear antibody (ANA); Rheumatoid factor (RF) and Human Immunodeficiency virus (HIV) came back negative.

Question 3

Based on the evidence presented, what would your diagnosis be?

Answer 3

Acute Interstitial Pneumonitis

After discussion with a tertiary centre, intravenous methylprednisolone was started, and this was later augmented with intravenous cyclophosphamide. Co-trimoxazole was started as fungal prophylaxis due to immunosuppression). This decreased his oxygen requirement mildly (saturations 92% on 28% high flow oxygen). A High-resolution-computed tomography (HRCT) done (3 months from his first admission) showed improvement, with some clearing of peripheral consolidation with evidence of fibrotic change in the lower lobes. Spirometry revealed a forced expiratory volume in the 1st second (FEV1) of 1.71 (46% predicted), forced vital capacity (FVC) 2.15 (46% predicted), with a ratio of 80%. Exercise capacity was significantly limited, and he managed less than 10 metres on the shuttle walking test as he felt extremely tired.

The departmental Interstitial Lung Disease Service concluded that the most likely diagnosis was acute interstitial pneumonia on clinical grounds, in reference to the radiology images, the negative microbiological results and the positive response to current treatment. A multidisciplinary team decision

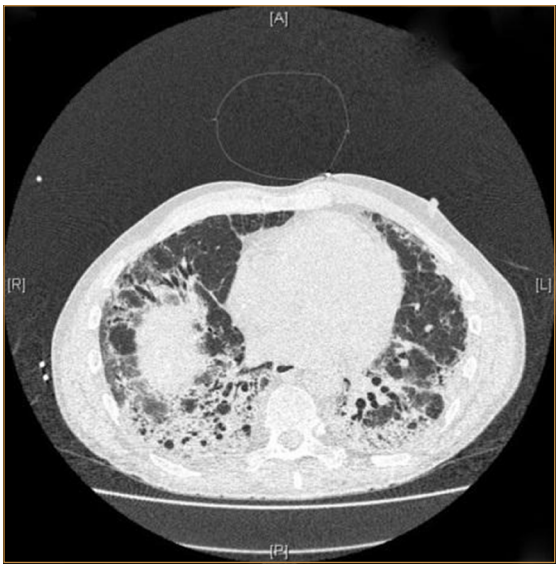

Figure 3.

was made in collaboration with the patient that the risks and discomfort the patient would have to undergo for performing a lung biopsy outweighed the prognosis and would not be in the patient's best interest and so to carry on with cyclophosphamide and prednisolone and to consider a repeat HRCT later to assess the patient's response, and to consider whether to further intensify treatment with mycophenolate. His exercise tolerance improved slowly and he was able to maintain his saturations to 96% on room air at rest 4-5 months after his initial presentation).

He had a repeat CT scan another 2 months later.

Question 4

What do you find on the repeat CT scan?

Answer 4

The repeat CT scan showed extensive fibrotic changes and ill-defined ground glass changes associated with bronchial dilatation and secondary lobular sparing in the lung bases. Some new nodular changes in the upper lobes was also reported.

He underwent bronchoscopy once more, and bronchooalveolar lavage was positive for parainfluenza and rhinovirus but negative for bacteria or Pneumocystis Jiroveci. It was considered possible that the new CT changes in the upper lobes were due to these viral infections and thus further stronger immunosuppressants such as mycophenolate was not given at the time due to risk of superimposed bacterial infection although steroids were continued as before.

The patient was reviewed regularly in respiratory clinic however there was no further improvement. His transfer factor performed a year and half later was 24% predicted and lung transplantation was discussed as there were no signs of any improvement in lung function parameters. He was assessed to be an ideal candidate for transplant however he wanted time to weigh his options. The patient used an oxygen concentrator at home 1 litre/ minute at night or when breathless. He also used ambulatory oxygen 1 litre/ minute. Unfortunately he was diagnosed with bladder carcinoma 6 months later and deemed to no longer be a candidate for transplantation.

His last admission in the hospital was approximately 4 years after the initial diagnosis. An echocardiogram showed evidence of pulmonary hypertension and severe right heart failure. His oxygenation was extremely poor and he did not respond to antibiotics and oxygen therapy. He passed away 3 days later. This was not reported to the Coroner and no post-mortem was held.

Discussion

Acute interstitial pneumonitis (also known as acute interstitial pneumonia (AIP) or Hamman-Rich Syndrome) is a rare, severe lung disease that usually affects healthy immune-competent individuals. It is a rare and fulminant form of lung injury originally described by Louis Hamman and Arnold Rich in 1935.[1] It falls under the category of both an interstitial lung disease (ILD) and a variant of acute respiratory distress syndrome (ARDS).[2] It is an ILD characterised by rapid onset respiratory failure similar to ARDS with diffuse alveolar damage (DAD) on biopsy specimen.[3]

There is no clear cause for this condition neither is there a cure. While the mechanism remains elusive, there are a few possibilities derived from recent studies. Specifically, both natural killer cells and chemokines such as IL-18 and IL-2 are the causative components behind the transformation of acute cell injury into interminable fibrosis due to the continuous abnormal wound repairing.[4] This is an animal study and in humans it is fairly speculative. AIP occurs most frequently among people older than forty years old and does not have a gender prevalence. Smoking is not associated with increased risk.[3-5]

Most patients describe an upper respiratory infection/viral-like prodrome and a non-productive cough.[3,6] About half of the patients present with fever, cough and shortness of breath[3] with negative results from bacterial and viral testing. A bimodal distribution exists, with about 50% of patients presenting within the first week of symptoms and others presenting up to 60 days from the onset of symptoms.[6] With rare exception, patients progress rapidly from shortness of breath to hypoxaemic respiratory failure that requires prolonged mechanical ventilation.

Sudden onset acute hypoxic respiratory failure in patient without pre-existing lung disease or extra-thoracic disorders should invoke the suspicion of ILD.[1,3,7] AIP radiologically and physiologically resembles ARDS[8,9] and idiopathic AIP should be considered as differential diagnosis of ARDS when a causative factor cannot be discovered. AIP is frequently confused with acute multi-lobar infectious pneumonia, with other forms of interstitial pneumonia, such as acute exacerbation of idiopathic pulmonary fibrosis (IPF), rapidly progressive bronchiolitis obliterans – organising pneumonia,[10] idiopathic acute eosinophilic pneumonia[2,11,12] and collagen-vascular diseases involving the lungs with primary or secondary pulmonary capillaritis.[13] Lung biopsy is confirmatory for AIP and it shows the organising form of diffuse alveolar damage (DAD) pattern.[3,14]

Due to the rarity of this entity, the clinical profile, laboratory data and treatment are not well defined.[15] Rapid progression from initial symptoms to respiratory failure is a key feature.[3,5,6] The chest x-ray and HRCT manifestations of AIP begin with a subtle increase in interstitial markings in the earliest phases which develops rapidly into a diffuse alveolar pattern which is bilateral and sometimes patchy and there are alveolar densities associated to areas of ground glass attenuation.[8] Traction bronchiectasis and bronchiectasis appear as the disease progresses.[16,17] Honeycomb fibrosis may be seen in the later phase of the disease. Patients with AIP tend to have a more symmetrical and lower zone distribution of abnormalities as well as more honeycombing than patients with ARDS.[18] Honeycomb change is not present early in the course of AIP and its identification on HRCT should prompt consideration of pre-existing fibrotic lung disease.[19]

The gross appearance is identical to ARDS and correlate with the stage of diffuse alveolar damage. In the early phase, the lungs are firm, heavy and have a homogenous dark red "beefy" appearance. In later phases, the lungs are extremely heavy with irregular areas of dense consolidation and fibrosis. Microscopic findings from the biopsy specimen from patients with AIP vary on the basis of the stage of the disease at the time of the biopsy. The initial stages starts with diffuse alveolar damage (organising phase).[20, 21] Figure IV is one such example.[22]

1. Interstitial oedema and numerous hyaline membranes are evident at low magnification
2. Fragments of hyaline membranes depicting organising phase of diffuse alveolar damage (taken from Bonaccorsi, A. *et al*. Acute interstitial pneumonia: report of a series *European Respiratory Journal* 2003 **21**: 187-19)

Biopsies that are taken later in the course of the disease resemble the honeycomb change of usual interstitial pneumonia, but fibroblastic proliferation, along with collagen deposition, is conspicuous within the walls of the air spaces.

In the intervening years since AIP's formal description in 1986, little progress has been made in the understanding of the disease. Currently, no specific or proven effective treatments for AIP exist, it is primarily supportive including supplemental oxygen[3, 23] and multidisciplinary team involvement is best for optional therapy. The need for mechanical ventilation is common. Broad-spectrum antibiotics and antiviral agents are often administered on an empirical basis. Therapy with high dose corticosteroids and cyclophosphamide are generally attempted. The use of intravenous glucocorticoids in treatment is considered to be beneficial[6,] although lacking in convincing support.[24] The only treatment that has met with success to date is a lung transplant.

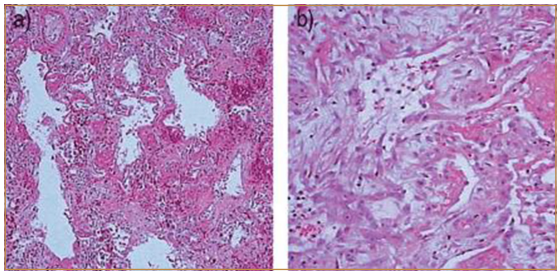

Figure 4.

Specific clinical or histological features that would predict survival have not been clearly identified.[3] Although relative differences in the radiographic features of patients with AIP and ARDS and AIP survivors versus non-survivors have been reported, these findings are difficult to extrapolate to prognosis for an individual patient. Survival data are limited and likely subject to some study bias, but the acute case fatality ratio is estimated to be 50% or more.[6,25] Most deaths (60%) occur within 1-6 months of diagnosis (median survival 1 ½ months),[2] whereas median survival for IPF patients is about 2- 5 years from the time of diagnosis.[23] Of those patients who survive, some return to their baseline respiratory function, but a significant proportion will exhibit some degree of functional respiratory impairment. Recurrent episodes of AIP have also been described. In general earlier intervention is associated with higher survival rates.[26]

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Abbreviations

AIP: Acute interstitial pneumonia
ANA: Anti-nuclear antibody
ANCA: Anti-neutrophil cytoplasmic antibody
ARDS: Acute respiratory distress syndrome
CT: Computerised tomography
CTPA: Computerised tomography pulmonary angiogram
DAD: Diffuse alveolar damage
FVC: Forced vital capacity
FEV1: Forced expiratory volume in the 1st second
HIV: Human Immunodeficiency virus
HRCT: High-resolution-computed tomography
IPF: Idiopathic pulmonary fibrosis
RF: Rheumatoid factor

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